

U.S.S.N 09/834,700

BRAUN

PRELIMINARY AMENDMENT AND RCE

AMENDMENTS TO THE SPECIFICATION:

IN THE SPECIFICATION:

Please amend the paragraphs on page 65, line 15 through page 66, line 4 as follows (insertions are underlined, deletions are in ~~strikeout~~):

Antisense compounds may be conveniently and routinely made through the well-known techniques technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates and alkylated derivatives.

Antisense compounds are typically 8 to 30 nucleotides in ~~length~~ length, are complementary to a targeted ~~to-a~~ nucleic acid molecule and ~~modulates~~ modulate its expression. The targeted nucleic acid molecule represents the coding strand. For example, for the AKAP10-5 allelic ~~variant~~ variant, an antisense compound is an antisense oligonucleotide that comprises the complement of at least an 8 nucleotide segment of SEQ ID NO: 3 including the nucleotide at position 2073 of SEQ ID NO: 3.

An antisense compound can contain at least one modified nucleotide that can confer nuclease resistance or increase the binding of the antisense compound with the target nucleotide. The antisense compound can ~~containing~~ contain at least one internucleoside linkage wherein the modified internucleoside linkage of the antisense oligonucleotide can be a phosphorothioate linkage, a morpholino linkage or a peptide-nucleic acid linkage.

Please amend the paragraph on page 65, lines 25-28 as follows:

An antisense compound can contain at least one ~~least-one~~ modified sugar moiety wherein the modified sugar moiety of the antisense oligonucleotide is a 2'-O-methoxyethyl sugar moiety or a 2'-dimethylaminoxyethoxy sugar moiety.

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Please amend the specification at page 70, beginning at line 20 as follows:

1. Correlation of an AKAP10 SNP with family history of heart disease

As noted above, using a healthy patient database (see, U.S. Provisional Application Serial No. 60/159,176 and U.S. Provisional Application Serial No. 60/217,658 and U.S. Application Serial No. 09/687,483 filed October 13, 2000), the frequency of occurrence of the AKAP10-5 SNP in such a population was found to decrease with age, thus making the allele a potential morbidity susceptibility gene, a gene associated with increased mortality or both. Using the healthy database, it was found that the homozygote GG genotype drops in the elderly population (over >60 years) by a statistically significant amount, p = 0.02.

The healthy database was then stratified (i.e., sorted) by information given by the donors about common disorders from which their parents suffered (the donor's familial history of disease). The study found that, in males 50 years and older, the AKAP10-5 allele is associated with cardiovascular disease. The subpopulation of donors 50 years and older was used in the study to insure that the parents were old enough to have potentially manifested the disease.

The frequency of the heterozygous genotype (A/G; ILE/VAL) showed an increase between none affected, one affected and both affected groups. For a disease that showed no correlation, there was no difference among these groups.

2. Correlation of an AKAP10 SNP with altered left ventricular function

The frequency of the AKAP10-5 SNP in DNA samples isolated from the blood of patients diagnosed with either coronary artery disease (CAD) or abnormal left ventricular (LV) function was investigated. These disorders were diagnosed in the patient population by cardiac catheterization. The left ventricle is the most important of the four chambers in the heart because it generates the pressure needed to circulate blood throughout the body. In addition, poor function of the left ventricle can be the indirect cause of other problems such as certain abnormal heart rhythms and stroke.

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The AKAP allele frequencies in the initial set of patient DNAs (145 patients), broken out by 3 clinical descriptors {ethnic group (white, hispanic or black), coronary artery disease (yes or no), and left ventricular function (normal or abnormal, as measured by reduced LV ejection fraction)} were calculated.

The results showed that the G allele appears to be more frequent in blacks > whites > hispanics, and more frequent in patients with abnormal LV function (a strong predictor of cardiovascular mortality). No apparent relationship with coronary artery disease was shown.